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Letter to the Editor

A personalized adhesion prevention strategy: E. Arslan, T. Talih, B. Oz, B. Halaclar, K. Caglayan, M. Sipahi, Comparison of lovastatin and hyaluronic acid/carboxymethyl cellulose on experimental created peritoneal adhesion model in rats, Int. J. Surg. 12 (2) (2014) 120–124.

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Dear Sir,

With great interest we have read the innovative study by Arslan et al. [1], which evaluates the adhesion prevention of the lovastatin and Seprafilm barriers. This study triggered some reflections.

The authors assume that the adhesion prevention impact of statins is related with their anti-inflammatory, antioxidant and antifibrotic properties [1]. In addition, they highlighted the pro-fibrinolytic impact of statins with increased activity of tissue type plasminogen activator (tPA) and down regulation of plasminogen activator inhibitor-1 (PAI-1) production by human mesothelial cells [2].

We fully agree with the authors' hypothesis of the supposed mechanisms of the adhesion prevention impact of statins [1], and we would like to extend the discussion and introduce our own concept about personalized postsurgical adhesion prevention strategy (Fig. 1) which takes into account possible predisposing (underlying coexisting) factors which might change postsurgical acute inflammation and wound healing features causing adhesion formation. Since an initial report concerning an experimental study aimed to investigate the effect of statins on postoperative adhesion formation [2] was followed by an editorial article in 'Ann Surg' by van der Wal and Jeekel [3], which discussed both possible benefits of statins as adhesion prevention medication and also possible harms of this medication due to well-recognized side effects of statins such as their myotoxicity and impairing liver and renal function. However, van der Wal and Jeekel [3]concluded that "this way of postoperative adhesion prevention is new and refreshing by interfering with the primary mechanism of adhesion formation".

An example of a possible primary predisposing metabolic mechanism of postsurgical complications may be a hyperhomocysteinemia, or/and deficiency of vitamin B12, B2 and folic acid, which promotes nitrous oxide (N_2O) anesthesia-induced postsurgical cardiovascular complications including a cardiac infarction [4–6]. Even a single exposure of N_2O during surgery as anesthetic medication could initiate postsurgical complications via an irreversible interaction of N_2O with vitamin B12. This interaction with changes in the cobalamin/methionine synthase and homocysteine metabolism may be fatal for individuals with predisposing genetic factors and is associated with neurotoxic, genotoxic (increased DNA damage) effects, endothelial dysfunction with elevated procoagulant status and increased risk of thromboembolism, atherosclerosis and cardiovascular diseases [4–8]. Subsequently, we recently reviewed the mechanisms [9] of a predisposing risk factor of increased postsurgical adhesion formation in a case of hyperhomocysteinemia through increased collagen formation between adhesion fibroblasts due to an elevated cysteine concentration [4–6] and by shift of the vascular endothelium surface from an anti- to pro-coagulant status, the reactivation of blood platelets, alterations of several intrinsic and extrinsic targets in the coagulation and fibrinolysis system with modification of the blood clot/fibrin clot structure with increased resistance of fibrin clot to fibrinolysis [7].

It is well known that peritoneal adhesions are initiated by surgical trauma and even after similar surgical procedures different outcomes can be found concerning postsurgical adhesions. Some individuals may have extended and severe postsurgical adhesions followed by complications which require repeated interventions, while others might not have any adhesions. The application of state of the art technologies has shown that some genetic and constitutional factors are associated with an increased susceptibility to postoperative adhesion formation.

Hence, we presume that there are predisposing genetic and constitutional conditions, which could change the character of dynamic postsurgical acute inflammation and wound healing mechanisms and play the role of coexisting factors, activating or inhibiting signaling pathways in the pathogenesis of peritoneal adhesions subsequently resulting in increased adhesion formation. Understanding of the impact of genetic and constitutional factors on adhesion formation allows us to suggest some basic principles of a personalized adhesion formation strategy (see Fig. 1). Therefore

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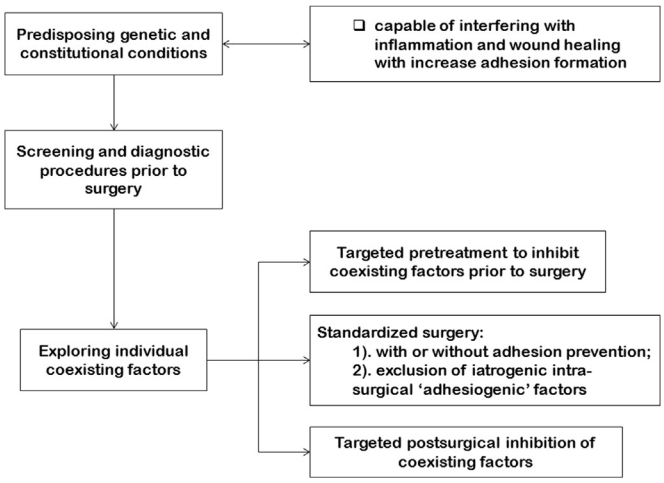

Fig. 1. A personalized adhesion prevention strategy with targeted elimination, inhibition and/or interlocking of coexisting adhesion initiating factors of postsurgical acute inflammation and wound healing.

screening and diagnostic procedures should explore these individual coexisting factors prior to surgery.

1. Genetic predisposition factors

Recent findings support a hypothesis that, in some individuals, an increased adhesion formation is associated with a genetic predisposition. Hence it was shown that an increased risk for adhesion formation is found in carriers of IL-1RN*2 allele [10].

On the other hand Tulandi et al. [11] presented an increased adhesion rate between the uterus and the bladder and between the uterus and the abdominal wall among women with keloid scarring (KS) after Cesarean section. These findings correspond with results supporting a strong genetic predisposition of some individuals to KS [12]. Then, a comparative genomic hybridization analysis of KS suggests a possible involvement of HLA class II histocompatibility antigen (HLA-DRB5) in a pathogenesis of KS [13].

Luo et al. [14] found an overexpression of a higher number of apoptotic-related genes in samples of KS and incisional scars, suggesting an increased rate of cellular turnover. Subsequently, apoptotic and non-apoptotic cell death is considered to increase local inflammatory reaction and is supposed to be a key step in tissue fibrosis. A number of genes functionally categorized as pro-inflammatory and pro-fibrotic mediators were identified in both KS and incisional scars [14]. These findings correlate with results of in vitro experiments which demonstrate that a microarray analysis of adhesions identifies specific genes with increased and decreased expression when compared with a normal peritoneum [15].

Many studies have addressed this issue by exploring novel biomarkers, genes, proteins, cytokines and mediators possibly involved in peritoneal adhesions [16–19]. It may help us gain more insight into the mechanisms of adhesion formation and suggest hypotheses and concepts taking into account signaling pathways based on the new findings [20,21].

Recently a way of genetic manipulation to prevent postsurgical adhesions was presented in a cell-culture model by modifications of reporter gene expression in human adhesion fibroblasts [22]. The adenovirus vector was designed to support the highest level of recombinant tissue plasminogen activator (rtPA) expression in human adhesion cells with minimal scarring [22] and this approach seems to be a promising adhesion prevention strategy for future studies.

2. Constitutional predisposition factors

Although many clinical observations have shown the impact of body mass index (BMI) on postsurgical outcome, recent studies examining the impact of obesity on outcomes of endoscopic procedures and several systemic reviews have yielded conflicting results.

Concerning the type of surgical procedures at the beginning of the "endoscopic era" complication rates for laparoscopic surgery (LS) on massively obese patients were higher than in the general population undergoing LS [23], then obesity was questioned as a high-risk factor for laparoscopic colorectal surgery [24]. Further studies of laparoscopic approach have shown that obese patients who are thought to be at increased risk of postoperative morbidity have the similar benefit as non-obese patients with colorectal [25] and gynecologic diseases [26].

However Siedhoff et al. [27] based on the retrospective cohort study including 834 patients who underwent laparoscopic hysterectomy, suggested that there is a significant association of BMI with surgical outcomes, and the effect is most pronounced in the morbidly obese ones. Akiyoshi et al. [28] found that the rate of postoperative complications was significantly higher in obese II patients than both in non-obese and obese I patients. Multivariate analysis showed that a BMI in the obese II range was an independent predictive factor for developing anastomotic leakage. Whereas, Mustain et al. [29] in their retrospective analysis of 9693 patients found significant differences among BMI classes for length of stay, operative time, and wound complication and confirmed that obesity is an independent risk factor for wound complications in patients undergoing laparoscopic colectomy.

An increased risk of wound infection complications has been confirmed in many studies, however an impact of BMI on adhesion formation was presented only by postmortem analysis [30]. By analyzing of 752 autopsies, Weibel and Majno [30] showed that the chances of postoperative adhesions developing are greater for a heavy woman if that woman is relatively short. Subsequently they concluded that as regards constitutional factors, short women who were also obese were especially prone to postoperative adhesions. These findings were contradicted with the existing, at that period predominant theory, that 'asthenic' individuals are more prone to the development of adhesions. Although the authors suggested that "large amounts of fatty tissue make the surgical procedure more difficult, longer, and more traumatizing, especially if the patient is relatively short" [30] unfortunately their concept was not evaluated.

Long ago a retrospective analysis was done as part of ScD thesis aiming to determine a relationship between BMI and pelvic adhesion extension rate (PAER) among 1152 women of reproductive age [31]. All patients had undergone prior surgeries, and then pelvic adhesions were evaluated during repeated surgery according to the pelvic adhesion classification system. Pelvic adhesions were defined as PAER 0 – absence of adhesions; PAER I degree – a few and light pelvic adhesions; PAER II degree – multiple, light and flat non vascularized pelvic adhesions and invisible <50% part of adnexa and/or uterus; PAER III degree – multiple, density, thick and vascularized pelvic adhesions and invisible >50% part of adnexa and/or uterus; PAER IV degree – multiple, density, thick and vascularized pelvic adhesions and invisible adnexa and/or uterus at all or "frozen pelvis". Briefly, 831 patients had experienced prior laparotomy and 221 patients – laparoscopic procedures. 49 patients had undergone only diagnostic procedures, whereas 1103 patients – various gynecological procedures or Caesarean sections. The total number of repeated surgical procedures was estimated at up to 14 and the fraction of prior single surgical procedures amounted to 57.8% in patients without adhesions,

whereas the percentages of the single procedures amounted to 50.0, 47.2, 44.2 and 39.0% in patients respectively with PAER I, II, III and IV. There was a direct positive correlation between increased weigh value and the PAER. Overweight was accompanied by an elevated PAER. On the contrary, there was a negative correlation between height and the PAER. Subsequently, increased height was accompanied by a reduced PAER [31,32].

Our previous results [31] are in accord with the postmortem data by Weibel & Majno [30] thereby supporting our current concept of personalized adhesion prevention strategy. However, in both of these studies surgical procedures had been performed in the past and the patient's weight was not known at the time of prior surgery, which is the main limiting factor. Therefore taking into account the limitations of these studies we suggest that the impact of BMI on postoperative adhesion formation calls for further investigations by prospective randomized studies with anthropometric patient parameters during initial surgery.

A possible impact of the obesity metabolism on adhesion formation can be linked by recent experimental studies which presented remarkable dysfunctions of macrophages caused by hyperglycemia and insulin deficiency, to which patients with diabetes are highly susceptible [33]. Macrophages were suggested to be a fundamental factor in triggering postsurgical adhesions [34–36], by the expression of pro-inflammatory cytokines.

In non-English literature, several genetic and constitutional conditions were suggested as increased adhesion predisposing factors, including so-called 'dense-vascularised' peritoneal adhesions formulated by an Italian team as "The simultaneous combination of high levels of exogenous female hormones (hormone replacement therapy or prolonged exposure to oral contraceptives) or endogenous hormones (as happens during pregnancy), a genetic predisposition (including genetic malformations) and previous surgery (peritoneal trauma), as evidenced in our patients, all seem to play a key role in the pathogenesis of so-called 'dense-vascularised', particularly tenacious adhesions responsible for the activation of multipotent mesenchymal submesothelial peritoneal cells" [37]. Many Russian researchers showed a rapid acetylation phenotype to be a pre-surgery screening-test for the prediction of the risk of postoperative adhesive complications and the need for preventive treatment [38,39].

Therefore, screening and diagnostic procedures may explore these individual coexisting factors prior to surgery such as in the PAPA- pilot study [40]. According to these findings, a personalized adhesion prevention strategy with targeted predisposing genetic and constitutional conditions, e.g., recommendations to decrease concentration of homocysteine, vitamin supplementations, folic acid, etc., may exclude or decrease the impact of these coexisting factors on acute inflammation and wound healing (see Fig. 1).

Standardized surgical procedures will be done with or without adhesion prevention depending on the individual predisposing condition of a given patient. Targeted postsurgical adhesion prevention may be implicated depending on an individual predisposing condition e.g., medication to increase local tPA [41], inhibit local PAI-1 [42], induce fibroblast apoptosis [43], and down regulate collagen cross linking [44,45], changing functional phenotype of peritoneal macrophages [46], local immunosuppression [20], application of genetic technologies [21,22] etc. In this case it is not necessary to use adhesion prevention barriers or other adjuvants in individuals with inhibited genetic and/or constitutional coexisting factors, when standardized minimally invasive surgical procedures were done.

It is important to emphasize that whenever surgical procedures are performed, both in adhesion high and low risk cases, a good practice is to prevent adhesions by a standardized surgical technique and simple measurements avoiding iatrogenic 'adhesiogenic' well-known factors such as use of towels, unnecessary manual intervention, excessive tissue trauma by electro/thermal coagulation and suturing, etc.

In conclusion, today we are at the beginning of a new era in medicine. In the near future upon accumulating evidence of genetic and constitutional predisposing factors by the-state-of-the-art screening and diagnostic tools and the reduction in price of these technologies, this strategy will become the dominating management strategy of postoperative adhesion prevention.

Ethical approval

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Author contribution

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Manuscript was drafted by OAM and has been critically revised by all authors: MYuE, AT, AM, IPK, MVM, TIB, MIM, ZhRK, MS, and a final revision was approved by all authors: OAM, MYuE, AT, AM, IPK, MVM, TIB, MIM, ZhRK, MS.

Conflicts of interest

None.

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O.A. Mynbaev*
The International Translational Medicine & Biomodeling Research Team, Department of Applied Mathematics, Moscow Institute of Physics & Technology (State University), Dolgoprudny, Moscow Region, Russia

The Department of Obstetrics, Gynecology & Reproductive Medicine, Peoples' Friendship, University of Russia, Moscow, Russia

Laboratory of Pilot Projects, Moscow State University of Medicine & Dentistry, Moscow, Russia

The New European Surgical Academy, Berlin, Germany

M. Yu Eliseeva
The Department of Obstetrics, Gynecology & Reproductive Medicine, Peoples' Friendship, University of Russia, Moscow, Russia

A. Tinelli
Department of Obstetrics and Gynaecology, Division of Experimental Endoscopic Surgery, Imaging, Minimally Invasive Therapy and Technology, Vito Fazzi Hospital, Piazza Muratore, Lecce, Italy

A. Malvasi
Department of Obstetrics and Gynecology, Santa Maria Hospital, Bari, Italy

I.P. Kosmas
Xatzikosta General Hospital, Ioannina, Ioannina, Greece

M.V. Medvediev
State Establishment "Dnepropetrovsk Medical Academy of Health Ministry of Ukraine", Dnepropetrovsk, Ukraine

T.I. Babenko
Stavropol State Medical Academy, Stavropol, Russia

M.I. Mazitova
Kazan State Medical Academy, Kazan, Russia

Zh. R. Kalzhanov
School of Health and Human Sciences, University of Essex, UK

M. Stark
The New European Surgical Academy, Berlin, Germany

* Corresponding author. The International Translational Medicine & Biomodeling Research Team, Department of Applied Mathematics, Moscow Institute of Physics & Technology (State University), Dolgoprudny, Moscow Region, Russia.
E-mail addresses: ospanmynbaev@hotmail.com, ospanmynbaev@list.ru (O.A. Mynbaev).

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